

17

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UPON THE EXTENT TO WHICH WIDAL'S REACTION PERSISTS AFTER RECOVERY FROM TYPHOID FEVER.

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INTRODUCTION.

It not infrequently happens that hospital patients present themselves with symptoms which suggest the possibility of typhoid fever, and yet give a history of having had typhoid fever, or some febrile attack which was thought to be typhoid fever, previously. The question at once arises whether a positive Widal's reaction in such cases favours the diagnosis of typhoid fever for their present trouble, or whether it may not be due to the former attack. The statements upon this subject in most text-books are very indefinite; sometimes the teaching is ¹² to the effect that the Widal test may remain positive for months and years after the typhoid fever; in other books,¹ that the reaction gradually diminishes in intensity until, after a few years, it disappears entirely.

THE WORK OF OTHERS.

There seem to be few statistics upon the matter. Widal himself¹³ repeated his test in seven cases one year after typhoid fever, and found the reaction negative in six, positive in one only. Laming Evans³ and Jörgensen⁶ both worked rather from the point of view of comparing the bactericidal with the agglutinative power of the serum than from that of observing how long it was possible to get a positive Widal's reaction after the fever was past. Evans, using the sedimentation method, repeated the Widal test in twenty-two patients at intervals of two to fourteen months after typhoid fever, and found it positive in five. Jörgensen, on the other hand, found the agglutinative power of the serum diminished very rapidly; it would rise again during a relapse, but when the typhoid fever was over he found the reaction became quite negative in a very few months. He expresses his results in the form of diagrams, Fig. 1 being a typical example.

At the end of this paper will be found references to articles by other observers who have repeated the Widal test in small numbers of patients, but nowhere have we been able to find any statistics covering a considerable number of consecutive cases.

THE SCOPE OF THE PRESENT WORK.

Wishing to find out what was the likelihood of a Widal reaction persisting for months, or years, after typhoid fever, we made a list of all the patients who had given positive reactions when ill with typhoid fever in Guy's Hospital; wrote to each patient; traced as many as we could; sent for these, or went to see them, and repeated the Widal test upon them in the usual way. Our difficulty has been to trace the patients. A great many hospital cases change their addresses frequently, and cannot be followed. Out of 281, we have been fortunate in finding 135 again.

The blood was taken in a Widal tube, and in each case sent to the Bacteriological Laboratory for examination in the routine

*Upon the Extent to which Widal's Reaction persists
after Recovery from Typhoid Fever.*

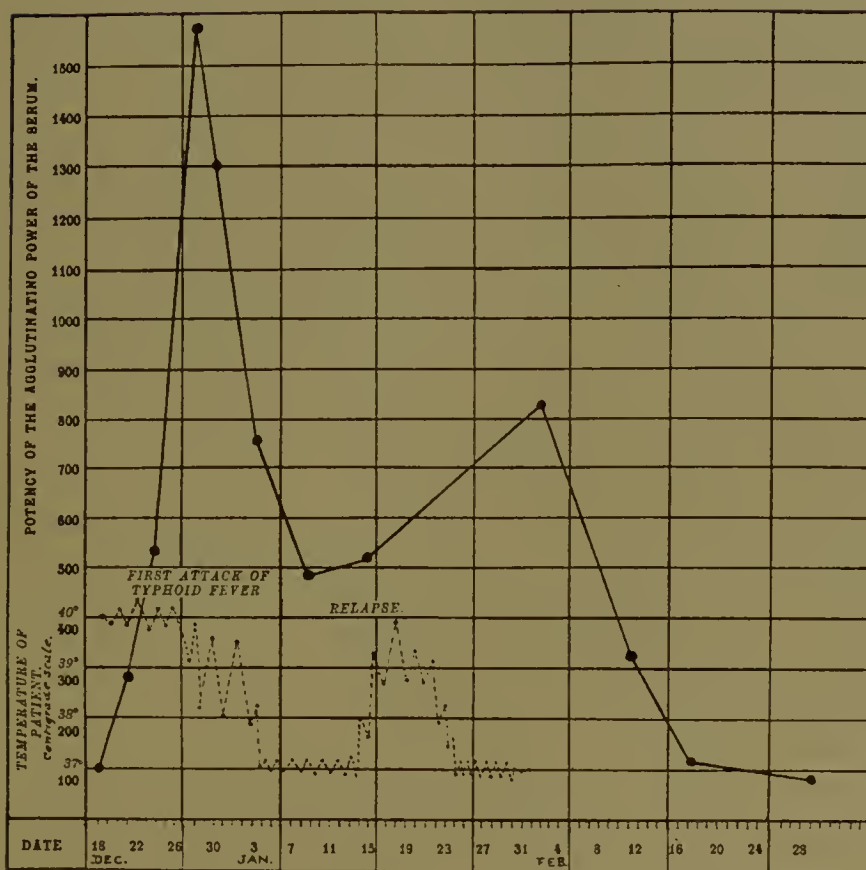


Fig. 1.—Diagram of agglutinative power of blood serum in relation to an attack of typhoid fever and to a relapse.

way. The method adopted was that of the hanging drop, with dilutions of the serum 1 in 20 and 1 in 200, as described in detail by Pakes.¹¹ The examining bacteriologist saw none of the patients, and had no knowledge as to whether the typhoid fever was recent or long past. The results, therefore, are exactly comparable to those that would be obtained in patients who were actually ill. In all cases the cultures of typhoid bacilli clumped readily with the serum of patients suffering from typhoid fever in the wards at the same time, and such patients served as controls throughout the research. Our best thanks are due to Dr. Eyre and Dr. Bainbridge both for carrying out some of the serum tests, and for valuable suggestions as to special points in the work.

THE STANDARD POSITIVE WIDAL'S TEST.

As Pakes¹¹ clearly showed, a positive Widal's reaction should be defined as a complete clumping of the typhoid bacilli within half an hour, when mixed with serum, the dilution being 1 in 200. He showed that out of 326 cases in which the Widal test was tried, 121 proved not to be typhoid fever, and not one of these gave the clumping in half an hour with 1 in 200 dilution of the serum. When less dilution is employed, clumping may be partial or complete, even when the patient has no typhoid fever. With a dilution of 1 in 20, for example, complete clumping within half an hour is not sufficient evidence, by itself, that the patient has typhoid fever; such reaction is suggestive, but it is only partial. In all our cases the Widal's test during the original typhoid fever was complete; that is to say, the patient's serum at that time clumped the typhoid bacilli in a hanging drop preparation within half an hour when the dilution of the serum was 1 in 200. We have kept to the same standard in repeating the test, every specimen being examined in dilutions of both 1 in 20 and 1 in 200, and the results recorded after the preparation had been

standing fifteen minutes and thirty minutes. Expressed as formulæ, the following represent the various degrees of reaction:—

1.—*Negative Reactions.*

Dilution of Serum. Per cent.	Minutes.			Per cent.	Minutes.		
	0.	15.	30.		0.	15.	30.
5	—	—	—	5	—	—	±
0·5	—	—	—	0·5	—	—	—

2.—*Partial Reactions.*

Dilution of Serum. Per cent.	Minutes.				Per cent.	Minutes.				Per cent.	Minutes.				Per cent.	Minutes.			
	0.	15.	30.			0.	15.	30.			0.	15.	30.			0.	15.	30.	
	5	—	—	+	5	—	±	+	5	—	+	+	5	—	±	+			
0.5	—	—	—	0.5	—	—	—	0.5	—	—	—	0.5	—	—	±				

3.—*Positive Reactions.*

Dilution of Serum. Per cent.	Minutes.			Minutes.			
	0.	15.	30.	Per cent.	0.	15.	30.
5	—	+	+	5	—	+	+
0.5	—	—	+	0.5	—	+	+

THE RESULTS OBTAINED.

The results obtained are given in a list at the end of the paper, grouped according to the degree of the reaction. The following table gives a summary of the total 135 cases:—

Table summarising the number of cases in each group, irrespective of the time that has elapsed between the original typhoid fever and the repetition of the Widal test:—

	Group A.	Group B.	Group C.	Group D.	Group E.	Group F.	Group G.	Group H.
	Minutes. 0 15 30 5 — — — 0.5 — — —	Minutes. 0 15 30 5 — — ± 0.5 — — —	Minutes. 0 15 30 5 — — + 0.5 — — —	Minutes. 0 15 30 5 — + + 0.5 — — —	Minutes. 0 15 30 5 — ± + 0.5 — — ±	Minutes. 0 15 30 5 — ± + 0.5 — — +	Minutes. 0 15 30 5 — + + 0.5 — ± +	Minutes. 0 15 30 5 — + + 0.5 — + +
Diluted serum, per cent. {								
Total Number in each group: (grand total 135)	81	13	14	10	6	7	3	1
Percentage of the total 135 in each group.	60	10	10	7.5	5	5	2.2	0.3
	Reaction negative. 70 per cent.			Reaction partial, in various degree. 22.5 per cent.			Reaction positive. 7.5 per cent.	

It thus appears that, although in the great majority the reaction becomes entirely negative after recovery from typhoid fever, a positive Widal's reaction may persist in 7·5 cases out of 100, whilst in 22·5 other cases there is a partial persistence of the reaction.

The question at once arises whether the persistence is only for a short time after the fever, or whether it may go on indefinitely. In the following table the cases are arranged according to the time that had elapsed between the typhoid fever and the repetition of the Widal's test:—

Table giving the percentage of negative, partial, and positive Widal reactions at various intervals after the original typhoid fever and positive reaction.

Interval between the original positive Widal's reaction and the time of its repetition.	Negative Reactions.		Partial Reactions.		Positive Reactions.		Total number of Cases.
	No. of Cases.	Per-centage.	No. of Cases.	Per-centage.	No. of Cases.	Per-centage.	
Between—							
1 month & 3 months	2	40	3	60	0	0	5
3 months & 6 months	4	67	2	33	0	0	6
6 months & 1 year	3	100	0	0	0	0	3
1 year & 2 years ...	14	78	4	22	0	0	18
2 years & 3 years ...	13	81	0	0	3	19	16
3 years & 4 years ...	7	100	0	0	0	0	7
4 years & 5 years ...	18	86	2	10	1	4	21
5 years & 6 years ...	12	67	5	28	1	5	18
6 years & 7 years ...	6	40	8	53	1	7	15
7 years & 8 years ...	7	54	2	15	4	31	13
8 years & 9 years ...	4	50	3	38	1	12	8
9 years & 10 years ...	4	80	1	20	0	0	5

It will be seen that time has very little influence upon it. Apparently, if the serum is going to retain its agglutinative power at all, it may do so for many years. In the above table it is obvious that the figures to be dealt with are far too small for any but the broadest conclusions to be drawn from them, but it is clear that the Widal's reaction may in many cases disappear in a very short time, and yet in a few may persist for well over eight years at least. The test has not been in vogue long enough for cases to have been followed up for periods of greater length than this.

Another question which arises is whether the age of the patient at the time of the typhoid fever has any effect upon the persistence of the Widal reaction. In the following table our cases are grouped according to age, and it is quite clear that the Widal reaction is no more likely to persist when the typhoid fever occurs at one age than it is at any other.

Table of cases, grouped according to the age of each patient at the time of the typhoid fever.

Age of patient at the time of the typhoid fever.	Negative Reactions now.		Partial Reactions now.		Positive Reactions now.		Total No. of Cases.
	No. of Cases.	Per-centage.	No. of Cases.	Per-centage.	No. of Cases.	Per-centage.	
5 years old or under	5	72	1	14	1	14	7
Between 5 & 10 years	25	76	6	18	2	6	33
" 10 & 15 years	19	83	3	13	1	4	23
" 15 & 20 years	20	67	8	27	2	6	30
" 20 & 30 years	13	59	6	27	3	14	22
" 30 & 40 years	11	58	6	31	2	11	19
" 40 & 50 years	1	100	0	0	0	0	1

When we investigate the influence of sex, however, we find that females appear much less likely to have a persistent Widal's reaction than are males :—

Table in which the cases are divided according to sex.

	Reaction Negative.		Reaction Partial.		Reaction Positive.		Total number of Cases.
	No.	Per-centage.	No.	Per-centage.	No.	Per-centage.	
Males	59	65	21	23	11	12	91
Females	35	80	9	20	0	0	44

It is true that the total number of cases should be much larger than our 135 to make the point absolutely certain. It is, we think, very unlikely that females never exhibit a persistent serum reaction; but seeing that 11 per cent. of our male, and not one of our female, patients had a persistent positive Widal's test, the above figures are probably more than mere coincidence.

In attempting to find some cause for the persistence of the positive reaction in those cases who had it, we made notes, before the blood was tested, of any prominent complications or sequelæ that were attributed by the patients to their typhoid fever. In the list at the end of the paper these are noted; when no note is made, it implies that the patient had had ordinary enterica without sequelæ. We have picked out the cases in which some suppurative lesion followed the fever, and tabulated them as follows:—

The influence of persistent typhoidal suppuration upon persistence of the positive Widal's reaction.

Widal's Reaction now negative.	{	Case No.		
		19	Post - typhoidal otorrhœa, still discharging from right ear.	} i.e., out of 94 negative cases, 3 had persistent suppuration = 3 per cent.
		46	Post - typhoidal otorrhœa, quiescent for 8 months.	
		85	Purulent discharge from right nostril ever since typhoid fever.	
Widal's Reaction now partial.	{		No case of persistent suppuration, post-typhoidal.	0.
Widal's Reaction still positive.	{	125	Post - typhoidal empyema, discharging for years.	} i.e., out of 11 positive cases, 3 had persistent suppuration = 27 per cent.
		128	Post - typhoidal otorrhœa, still discharging from both ears.	
		130	Post - typhoidal otorrhœa, still discharging from both ears.	

It will be seen that, although post-typhoidal suppuration, such as otitis media or empyema, seems to render the patient rather more liable to a persistent Widal reaction, the latter may persist without any such cause; and as far as we have been able to judge there is no clinical means of picking out those cases in which the Widal reaction will persist from those in which it will not. This agrees with the views of Jörgensen⁶ and others, namely, that the activity of the serum reaction bears no direct relation to the severity of the disease.

CONCLUSIONS.

Our conclusions are:—

1. That in most cases the Widal's reaction disappears rapidly after the typhoid fever.
2. That in 7.5 per cent. of our cases it remains positive, and may remain so for over eight years, and we do not know how much longer.
3. That the age of the patient at the time of the typhoid fever has little or no influence on the likelihood of this persistence of the Widal's reaction.
4. That the Widal's reaction is apparently more liable to persist in males than it is in females.
5. That the presence of post-typhoidal suppuration somewhat increases the likelihood of this persistence, but is not its only cause.
6. That the cause of the persistence is not known in most cases; and that it is not possible, clinically, to say which patient will, and which will not, give a positive Widal's reaction for years after typhoid fever.
7. That in any given patient, therefore, in whom the present symptoms might be due to typhoid fever, and in whom there is a possibility of a previous attack, the presence of a complete positive Widal's reaction will leave a 7.5 per cent. doubt as to whether this reaction is due to former enterica rather than to the present illness. The great probability is that a complete positive Widal's reaction indicates present typhoid fever.

*Table of cases in which the Widal test with Bacillus Typhosus was repeated months or years after the Widal test was positive during Typhoid Fever.**

GROUP A.†

Cases in which no reaction occurred even in the serum diluted only 1 in 20.

<i>i. c.</i>	Dilution of serum.	Minutes.			
		Per cent.	0	15	30
		5	—	—	—
		0·5	—	—	—

*The cases were all clinically undoubted cases of typhoid fever. By "positive Widal's test" is understood clumping of the *Bacillus Typhosus* within half an hour when mixed with serum diluted 1 in 200 (Pakes).

† Groups A & B are "negative reactions."

Groups C, D & E are "partial reactions."

Groups F, G & H are "positive reactions."

Case Number.	Sex of patient.	Age of patient at the time of the typhoid fever.	Interval between original positive Widal reaction and the time of repetition of the Widal test.			Special Remarks.
			Years.	Years.	Mths.	
1	M	14	9	9		Had typhoid fever twice : once in 1895, again in 1897. Was in Guy's Hospital with each attack.
2	F	35	9	5		Married.
3	F	9	9	5		
4	M	20	9	2		
5	M	29	8	11		
6	M	20	8	4		
7	M	20	8	1		
8	M	10	8	0		
9	M	10	7	10		
10	F	20	7	6		Married.
11	M	16	7	5		
12	F	13	7	5		
13	F	27	7	2		Single.
14	M	33	6	9		
15	M	35	6	8		
16	M	12	6	7		
17	M	6	6	7		Blepharitis ; little or no discharge.
18	M	6	6	3		
19	F	5	6	0		Otitis media after typhoid ; right ear still discharges.
20	M	17	5	11		
21	F	39	5	10		Married.
22	M	17	5	10		
23	F	12	5	10		
24	M	5	5	8		
25	M	5	5	7		
26	M	10	5	7		
27	F	32	5	7		Single.
28	M	16	5	4		
29	M	31	5	3		
30	F	11	5	2		
31	M	12	5	0		
32	F	7	4	11		
33	M	19	4	10		
34	M	11	4	10		
35	F	11	4	9		
36	M	9	4	9		Brother of 35.
37	F	26	4	8		Married.
38	F	8	4	8		Has chorea and endocarditis.
39	M	16	4	7		
40	M	19	4	6		
41	F	8	4	5		Just convalescent from severe scarlatina.
42	M	12	4	4		
43	M	7	4	3		
44	F	22	4	3		Married.
45	F	31	4	2		Married.

Case Number.	Sex of patient.	Age of patient at the time of the typhoid fever.	Interval between original positive Widal reaction and the time of repetition of the Widal test.			Special Remarks.
			Years.	Years.	Mths.	
46	M	18	4	1		Had had otorrhœa for three and a half years, post-typhoidal. It stopped 8 months ago.
47	M	18	4	1		
48	F	5	4	0		
49	M	12	3	11		
50	M	6	3	11		
51	F	18	3	9		Single at the time of typhoid fever. Married now.
52	F	31	3	8		Married.
53	F	26	3	7		Pregnant 6 months when Widal repeated.
54	F	28	3	3		Single.
55	M	28	3	0		
56	M	41	3	0		
57	M	21	3	0		
58	M	13	3	0		
59	M	7	3	0		Has many glands in neck, ? tuberculous.
60	F	14	3	0		
61	M	10	2	11		
62	M	19	2	7		
63	M	9	2	7		
64	F	25	2	6		Single.
65	M	9	2	3		
66	M	12	1	10		
67	M	10	1	9		
68	M	17	1	8		
69	F	28	1	8		Married.
70	F	27	1	5		Married.
71	F	15	1	4		
72	M	6	1	4		Has double otitis media, but this dates from scarlatina at two.
73	F	21	1	4		Single.
74	M	6	1	3		
75	M	6	1	2		
76	M	9	1	0		
77	M	7	0	7		
78	F	5	0	6		"Chest bad, and going thin."
79	F	10	0	4		
80	F	16	0	2		
81	M	12	0	2		

GROUP B.

Cases in which an indefinite reaction occurred in 30 minutes with serum diluted 1 in 20, but no reaction occurred with serum diluted 1 in 200; nor with 1 in 20 in less than 30 minutes.

<i>i. c.</i>	Dilution of serum.	Minutes.			
		Per cent.	0.	15.	30.
		5	—	—	±
		0.5	—	—	—

Case Number.	Sex of patient.	Age of patient at the time of the typhoid fever.	Interval between original positive Widal reaction and the time of repetition of the Widal test.			Special remarks.
		Years.	Years.	Mths.		
82	M	13	8	1		Has frequent epileptic fits.
83	M	17	7	10		
84	M	12	6	6		
85	M	35	4	5		Has had purulent discharge from right nostril ever since typhoid fever.
86	M	12	2	3		
87	F	32	2	2		Married.
88	M	13	2	0		
89	M	10	1	11		Brother of 66.
90	M	9	1	7		
91	F	26	1	2		Married.
92	F	38	0	11		Married. Was pregnant during typhoid. Baby born dead later.
93	F	17	0	5		Single.
94	M	16	0	4		

GROUP C.

Cases in which a definite reaction occurred in 30 minutes with serum diluted 1 in 20, but no reaction occurred with serum diluted 1 in 200; nor with 1 in 20 in less than 30 minutes.

i. e.	Dilution of serum.	Minutes.			
		Per cent.	0.	15.	30.
		5	—	—	+
	0.5	—	—	—	—

Case Number.	Sex of patient.	Age of patient at the time of the typhoid fever.	Interval between original positive Widal reaction and the time of repetition of the Widal test.		Special Remarks.
			Years.	Years. Mths.	
95	M	13	8	4	
96	M	25	8	2	
97	F	20	7	1	Single.
98	F	31	6	10	Married. Is convalescing from influenza.
99	F	24	6	10	Married.
100	M	26	6	9	
101	F	6	6	9	
102	M	8	6	0	
103	F	22	5	9	Married. Is now pregnant
104	M	5	5	4	
105	M	21	5	2	
106	M	19	4	5	
107	F	18	1	1	Single.
108	M	18	0	5	Cough ever since. Looks well.

GROUP D.

Cases in which a definite reaction occurred in 15 minutes with serum diluted 1 in 20, but no reaction occurred with serum diluted 1 in 200.

<i>i. e.</i>	Dilution of serum.	Minutes.			
		Per cent.	0.	15.	30.
		5	—	+	+
		0.5	—	—	—

Case Number.	Sex of patient.	Age of patient at the time of the typhoid fever.	Interval between original positive Widal reaction and the time of repetition of the Widal test.			Special Remarks.
			Years.	Years.	Mths.	
109	M	10	9	3		Has bad acne of face and back.
110	M	9	8	7		
111	M	16	7	1		
112	M	31	6	10		Has had bad Malta fever since ; also vesical calculus.
113	M	7	6	6		
114	M	17	6	5		
115	M	21	6	5		
116	M	19	5	9		
117	F	13	4	3		
118	M	32	0	1		

GROUP E.

Cases in which an indefinite reaction occurred with serum diluted 1 in 200, in 30 minutes.

<i>i. e.</i>	Dilution of serum.	Minutes.			
		Per cent.	0.	15.	30.
		5	—	±	+
	0·5	—	—	±	

Case Number.	Sex of patient.	Age of patient at the time of the typhoid fever.	Interval between original positive Widal reaction and the time of repetition of the Widal test.			Special Remarks.
		Years.	Years.	Mths.		
119	M	38	1	6		
120	M	6	1	3		Has a cardiac lesion.
121	F	34	1	2		Rheumatism and dyspepsia ever since.
122	M	13	0	4		
123	F	17	0	3		Single.
124	M	37	0	3		

GROUP F.

Cases in which a definite reaction occurred with serum diluted 1 in 200 in 30 minutes ; but no reaction occurred with 1 in 200 in 15 minutes.

<i>i. e.</i>	Dilution of serum	Minutes.			
		Per cent.	0.	15.	30.
		5	—	±	+
		0·5	—	—	+

Case Number.	Sex of patient.	Age of patient at the time of the typhoid fever.	Interval between original positive Widal reaction and the time of repetition of the Widal test.		Special Remarks.
			Years.	Years. Mths.	
125	M	34	8	1	Empyema followed typhoid. The sinus discharged till quite recently, though to-day it was healed over.
126	M	8	7	9	Double otitis media after typhoid, still discharging occasionally.
127	M	25	7	8	
128	M	17	7	5	
129	M	28	6	10	Double otitis media after typhoid. Had mastoid operation in London Hospital 9 months ago. Both ears discharge occasionally still.
130	M	11	5	10	
131	M	7	2	7	

GROUP G.

Cases in which a definite reaction occurred with serum diluted 1 in 200 in 30 minutes; and a partial reaction occurred with 1 in 200 in 15 minutes.

i. e.			Dilution of serum.				Minutes.			
			Per cent.		0.	15.	30.			
			5		—	+	+			
			0.5		—	±	+			
Case Number.	Sex of patient.	Age of patient at the time of the typhoid fever.	Interval between original positive Widal reaction and the time of repetition of the Widal test.		Special Remarks.					
		Years.	Years.	Mths.						
132	M	21	4	1	Just convalescent from influenza.					
133	M	16	2	4						
134	M	33	2	4						

GROUP H.

Case in which a definite reaction occurred with serum diluted 1 in 200, in 15 minutes.

Case Number.	Sex of patient.	Age of patient at the time of the typhoid fever.	Interval between original positive Widal reaction and the time of repetition of the Widal test.	Special Remarks.	<i>i. e.</i>	Dilution of serum.	Minutes.			
					Per cent.	0.	15.	30.		
					5	—	+	+		
					0.5	—	+	+		
135	M	3	7 8							

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